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**Please find below and/or attached an Office communication concerning this application or proceeding.**

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Attachment to the Advisory Action:

Applicant's arguments filed on 07/28/2008 have been fully considered but they are not persuasive.

With respect to the rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Drysdale et al. Applicant argues that, Drysdale et al. do not teach a method of forming autonomically beating cardiac muscle-like cell aggregates from stem cells, and teach an embryo that is not treated with RA (retinoic acid) will give rise to cardiac tissue, while treatment of an embryo with RA will induce dysfunction of cardiac tissue due to possible suppression of a differentiating factor by RA.

However, Drysdale et al. disclose in RA-treated mouse embryos a beating heart forms (p.213 1st column 2nd paragraph lines 10-13). Drysdale et al. therefore clearly anticipate the claimed method.

Applicant further argues that Drysdale et al. do not teach pluripotent stem cell capable of generating a number of different cell types, and do not culture stem cells.

However, according to the specification page 6 last paragraph, especially lines 5 and 7, stem cells such as embryonic stem cells and embryoid bodies can be used, and as mentioned before and immediately above, Drysdale et al. disclose culturing cells removed from embryo (explants) and embryos. Therefore, Drysdale et al. disclose culturing stem cells.

With respect to the rejection of claims 1-3 under 35 U.S.C. 103(a) over Drysdale et al. in view of Takahashi et al. Applicant argues that there is no reason to modify or combine the teachings of Drysdale et al. with Takahashi et al. to arrive at the presently claimed invention.

As mentioned immediately above, Drysdale et al. teach a method of forming autonomically beating cardiac muscle-like cell aggregates from stem cells, culturing stem cells derived from a vertebrate animal in the presence of retinoic acid or RA (RXR agonist). Drysdale et al. also teach heart development and myocardial differentiation are sensitive to RA signaling (Abstract and p.206 1st column 2nd and 3rd paragraphs). Drysdale et al. further teach RA can block myocardial differentiation in a stage-specific manner (p.211 1st column 3rd paragraph), depend on the effective dose of RA (p. 212 2nd column end paragraph lines 13-14 continued to p.213 1st column line 1). Drysdale et al. teach if RA treatment initiated after myocardial differentiation has commenced there is no discernible effect on the subsequent heart development (p.206 1st column 3rd paragraph 6-9).

Drysdale et al. do not teach RXR agonist is PA024 or 2-[N-cyclopropyl-methyl-N-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethynaphtahlene-2-yl)amino]pyrimidin-5-carboxylic acid). However, Takahashi et al. teach RXR agonist, PA024, and stem cell differentiation inducing activity of PA024 and selective antagonism at RXR site (Abstract. p.3328 Chart 1., p.3329 1st column 2nd paragraph, lines 10-17).

Therefore, a person of ordinary skill in the art at the time the invention was made, knowing the stem cell differentiation inducing activity and selective antagonism of PA024 at RXR site, would have been motivated to substitute the retinoic acid X receptor (RXR) ligand in the method as taught by Drysdale et al. with RXR agonist according to

the teachings of Takahashi et al. to provide a method for forming autonomically beating cardiac muscle-like cell aggregation form stem cells derived from a vertebrate animal *in vitro* with predictable results of inducing the differentiation of stem cells, because substitution of one known RXR agonist with another known RXR agonist would have given predictable results to a person of ordinary skill in the art at the time the invention was made.

With respect to the rejection of claim 7 under 35 U.S.C. 102(b) as being anticipated by Moriya et al. Applicant argues that the embryonic ectoderm disclosed in Moriya et al. is different from the claimed embryonic stem cells and are not stem cells.

However, applicant fails to show how, because specification page 6 last paragraph especially lines 5 and 7, disclose stem cells such as embryonic stem cells and embryoid bodies can be used. As mentioned in the Final Office action, Medical dictionary online (11 March 2008) defines ectoderm, the outer layer of the three germ layers of the embryo. Therefore, Moriya disclosure of isolated ectoderm region meets the claimed stem cells derived from a vertebrate animal.

With respect to the rejection of claims 7 and 8 under 35 U.S.C. 103(a) as being unpatentable over Moriya et al. in view of Takahashi et al. Applicant argues that there is no reason to modify or combine the teachings of Moriya et al. and Takahashi et al. to arrive at the presently claimed invention.

However, Moriya et al. teach the isolated ectoderm region differentiated into pancreas when cultured in the presence of retinoic acid receptor (RAR ligand) (Abstract).

Moriya et al. do not teach the retinoic acid receptor (RAR) ligand is 4-[(5, 6, 7, 8,-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl] benzoic acid. However, Takahashi et al. teach retinoic acid receptor (RAR) ligand (agonist) Am80 (or 4-[(5, 6, 7, 8,-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl] benzoic acid) (Abstract). Takahashi et al. teach a combination of Am80 with an RXR ligand (agonist) induce differentiation of stem cells (p.3328 2$^{nd}$ column end paragraph). Takahashi et al. further teach the clinical potential of compounds (RXR antagonists) that inhibit the activation of retinoic acid receptors (RARs) induced by RAR agonists, as antidiabetic and antiobesity agents (p.3327 2$^{nd}$ column 1$^{st}$ paragraph lines 8-15).

Therefore, a person of ordinary skill in the art at the time the invention was made, knowing that a combination of retinoic acid receptor (RAR) ligand and a RXR ligand induce differentiation of stem cells, would have been motivated to apply the prior art teachings an to use the retinoic acid receptor (RAR) ligand as taught by Takahashi et al. in the method of Moriya et al. to provide a method for forming a tissue having morphology and function of pancreas from stem cells derived from a vertebrate animal with a reasonable expectation of success.